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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/[illegible]778	12/98	ARIYOSHI	ARIYASU=1

HM22/1004

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EXAMINER	
KAUFMAN, C	

ART UNIT	PAPER NUMBER
1646	#10

DATE MAILED: 10/04/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/063,778	Applicant(s) ARIYASU ET AL.	
	Examin r Claire M. Kaufman	Art Unit 1646	

-- Th MAILING DATE of this communication app ars on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *July 13, 1999* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *7-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-22* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,7* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that examination of plural groups would not involve a serious burden because (1) consideration of the protein would require consideration of the DNA and method of producing the protein and (2) an antibody is not patentably distinct from the protein as it is obvious over the protein. This is not found persuasive because with respect to point (1), the inventions are distinct because the protein may be produced by means other than expression of the full-length protein (*e.g.*, chemical synthesis), and a search for the full-length encoding nucleic acid is not required for a search of the invention of Group I. Further, the recombinant method producing the protein Group I (*i.e.*, method in Group II) does not require searching for anticipatory art for the protein itself, which is not true for the protein search. Additionally, as previously stated the different classifications support the need for different searches for each group. With respect to point (2), a search for the protein does not require a search for the antibody, though the reverse is not true. Additionally searching requires more than identification of art over which the invention is obvious, it requires searching for anticipatory art. Obviousness alone in this situation is not a sufficient grounds for removing a restriction. Further, the fact that the antibody of Group III may bind to proteins other than human Desert hedgehog, *e.g.*, Sonic hedgehog--see claim 15, means that the search for the antibody requires searches of proteins in addition to the claimed protein, which searches are not required for the protein claimed. For these reasons, the inventions are distinct.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The specification is replete with grammatical and idiomatic errors too numerous to mention specifically. The specification should be revised carefully. Examples of such errors are: p. 2, line 7, "are" should be --is--; p. 3, line 5, "cheked" should be --checked--, p. 3, line7, "he said to know" is incorrect.

Appropriate correction is required.

Applicants are required to use the heading "Brief Description of the Drawings" instead of "Brief Explanation of the Accompanying Drawings" at page 4. See MPEP 608.01(f)

The use of several trademarks (*e.g.*, GenBank, SuperScript) has been noted in this application. Trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. For example, in the last line of page 2, the trademark does not appear capitalized, but instead has "®", and on page 30, 3 lines from the bottom, "™" appears without capitalization of the name.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Since the claimed DNA is naturally occurring and is not claimed as purified and/or isolated, the claims do not show the hand of man involved in the invention and, therefore, are unpatentable. See MPEP § 706.03(a) and 2105.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. When biological material is required to practice an invention, and if it is not so obtainable or available, the enablement requirements of 35 USC §112, first paragraph, may be satisfied by a deposit of the material. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining human cell line ARH-77, ATCC CRL-1621 for the life of the patent if this application issues as a patent, and it does not appear to be a readily available material. Deposit of the cell line in accordance with the required regulations discussed below would satisfy the requirements of 35 USC §112, first paragraph. For each deposit made pursuant to these regulations, the specification shall contain: (1) The accession number for the deposit; (2) The date of the deposit; (3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and (4) The name and address of the depository. [See MPEP 2404-2410.02]

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or Declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating

that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification. In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 6 and dependent claims 3-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 are indefinite because it is unclear what distinguishes a Desert hedgehog (Dhh) protein from other proteins, particularly other hedgehog proteins. As a result, the metes and bounds of the claim is not clear. There are no characteristics by which one could distinguished the Dhh protein of the instant invention from other proteins. Note that claims 2-4 require only that it contain a part of a specified amino acid sequence. As a part can be one amino acid, almost all proteins comprise at least one amino acid in common with the sequences listed. For these reasons, the metes and bounds of the claims cannot be determined.

Claims 1 and 5 are indefinite because it is unclear how the hedgehog protein of claim 5 which originates from a human cell is different from the hedgehog protein of human origin of

claim 1. If there is a difference, then that should be clear. If there is not, then the claims are substantially duplicative of each other.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tate et al. (U, GenBank Accession No. AB010994) in view of Korsmeyer (A, US Patent 5,955,595) and Ingham et al. (B, US Patent 5,844,079).

Tate et al. teach the complete encoded amino acid sequence of a human desert hedgehog protein and part of the encoding DNA sequence. Tate et al. do not teach the expressed protein.

Korsmeyer teach that chemical synthesis of polypeptides is well known in the art and provides references for guidance (col. 20, lines 45-59).

Ingham et al. teach mouse Desert hedgehog (Dhh, SEQ ID NO:9), mouse and human Indian hedgehog (Ihh, SEQ ID NO: 14 and 10, respectively), and mouse, chicken, human and zebrafish Sonic hedgehog (Shh, SEQ ID NO: 11, 8, 13 and 12, respectively). Cross-species sequence comparison of Ihh and Shh are made to estimate where in the proteins essential activity resides (*e.g.*, col. 81, lines 35-47). The effect of Shh on neural tube tissue explants was also tested to determine the effect on motor neuron inducing activity (Example 9, col. 106).

It would have been obvious to produce the human Dhh protein having the amino acid sequence taught by Tate et al. using one of the well known chemical synthesis methods discussed by Korsmeyer. One would have been motivated to do so to be able to perform cross-species comparisons with Dhh as described by Ingham for Ihh and Shh to suggest where critical regions in the protein are or to determine what effect Dhh had on neurons.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drummond (AG cited by Applicants, also known as GenBank Accession No. U59748) and Ingham et al. (B, US Patent 5,844,079).

Drummond teaches part of the nucleic acid encoding human Dhh and the corresponding deduced amino acid sequence. Drummond does not teach the expressed protein.

Ingham et al. teach mouse Desert hedgehog (Dhh, SEQ ID NO:9), mouse and human Indian hedgehog (Ihh, SEQ ID NO: 14 and 10, respectively), and mouse, chicken, human and zebrafish Sonic hedgehog (Shh, SEQ ID NO: 11, 8, 13 and 12, respectively). Also taught are methods of obtaining the full-length encoding nucleic acid from primers derived from known fragments of a sequence (Example 1), as well as in vitro expression of the encoded protein (*e.g.*, col. 88, lines 17-59). Cross-species sequence comparison of Ihh and Shh are made to estimate where in the proteins essential activity resides (*e.g.*, col. 81, lines 35-47). The effect of Shh on neural tube tissue explants was also tested to determine the effect on motor neuron inducing activity (Example 9, col. 106).

It would have been obvious to obtain the full-length coding region of the human Dhh nucleic acid of Drummond using one of the methods of Ingham et al. and to express the protein as taught for other hedgehog proteins by Ingham et al. One would have been motivated to do so to be able to perform cross-species comparisons with Dhh as described by Ingham for Ihh and Shh to suggest where critical regions in the protein are or to determine what effect Dhh had on neurons.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Epstein et al. (C, US Patent 5,759,811) describe a single mutation in human Shh associated with tumorogenicity, the existence of a partial nucleic acid sequence of human Dhh and the desire to test hedgehog proteins besides Shh for the ability to promote tumor growth.

Conclusion

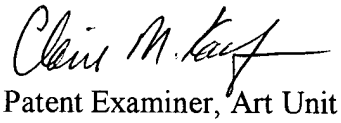
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

September 22, 1999